

A Highly Enantioselective and Diastereoselective Synthesis of Cyclobutanes via Boronic Esters

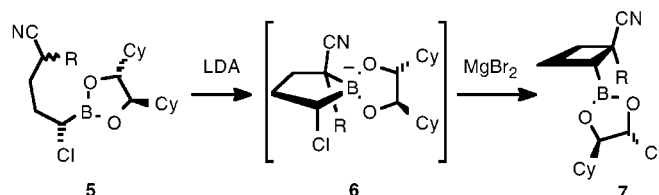
Hon-Wah Man, William C. Hiscox, and Donald S. Matteson*

Department of Chemistry, Box 644630, Washington State University,
Pullman, Washington 99164-4630

dmatteson@wsu.edu

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ABSTRACT



Deprotonation of enantiopure (*R,R*)-1,2-dicyclohexyl-1,2-ethanediol 1-chloro-4-cyanobutylboronates **5** with LDA followed by treatment with anhydrous magnesium bromide yields (*R*)-(*trans*-2-cyanocyclobutyl)boronic esters **7** in high diastereomeric and enantiomeric purity. No cyclobutane formation has been observed in the absence of at least a catalytic amount of magnesium halide.

We have found a highly enantioselective and diastereoselective general synthesis of cyclobutanes having two or three stereocenters in the ring, which utilizes asymmetric (4-cyano-1-chlorobutyl)boronic esters as the key intermediates. α -Chloro boronic esters have previously been shown (1) to be capable of providing exceptionally high stereocontrol in the construction of asymmetric centers¹ and (2) to allow the assembly of molecules containing several adjacent stereocenters bearing a variety of functional substituents.² However, this chemistry has not been used for the preparation of carbocycles.

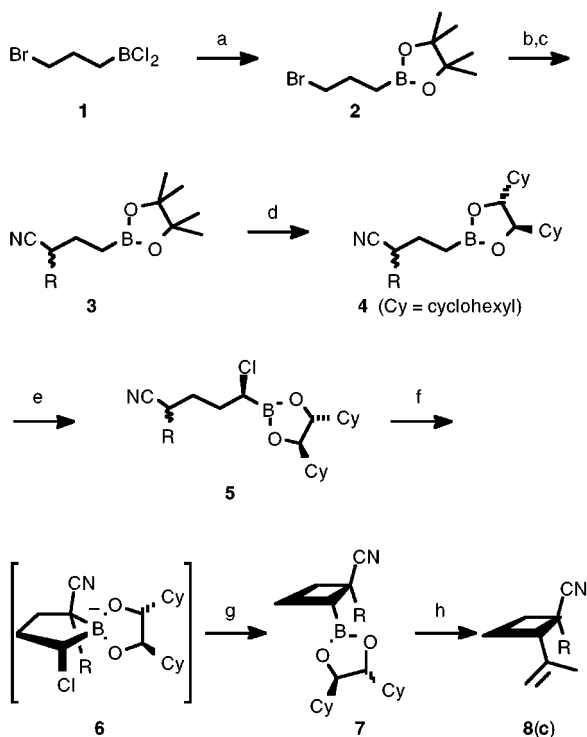
The reaction of allyl bromide with boron trichloride and triethylsilane was used to prepare (3-bromopropyl)dichloroborane (**1**),³ which was converted to pinacol (3-bromopro-

pyl)boronate (**2**). Treatment of **2** with sodium cyanide in DMSO then yielded **3a** (R = H), which was transesterified with (*R,R*)-1,2-dicyclohexyl-1,2-ethanediol⁴ to make boronic ester **4a** (Scheme 1).

Chain extension of **4a** with (dichloromethyl)lithium according to the established method^{1,2} yielded chloro boronic ester **5a** (R = H). Cyclization of **5a** was initially accomplished by treatment with commercial lithium diisopropylamide (LDA).⁵ Presumably the cyclic borate **6a** is formed immediately, but ring contraction with carbon-carbon bond formation is very slow. Yields of **7a** up to ~65% (containing ~6% cis isomer) were obtained irreproducibly. Dark batches of LDA yielded only ~20%, and LDA freshly prepared from butyllithium and diisopropylamine failed entirely. We then noted that our purchased LDA solutions contained a small amount of magnesium diisopropylamide as a stabilizer. Addition of 0.1–1.0 equiv of anhydrous magnesium bromide in THF (from 1,2-dibromoethane and magnesium) after the

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Scheme 1^a

a, R = H; b, R = CH₃; c, R = (CH₂)₂OSiMe₂t-Bu

^a (a) Pinacol, ether, -78 °C; (b) NaCN in DMSO, 50 °C, 12 h; (c) if H replaced by R (series b, c), LDA in THF, -78 °C; R-I; (d) (*R,R*)-1,2-dicyclohexyl-1,2-ethanediol; (e) LiCHCl₂ in THF, -100 °C; ZnCl₂; to 25 °C 16–24 h; (f) LDA, -78 °C; (g) MgBr₂, THF, 3 days; (h) isopropenyl-MgBr, -78 °C; I₂, Mg(OMe)₂.

LDA resulted in very high yields of **7a** routinely, and the cis isomer was not detected by NMR, implying that <2% could be present.

To enter series **b** or **c**, cyanopropylboronic ester **3a** (or **4a**) was deprotonated with LDA and treated with the alkyl iodide. Prior to the discovery of magnesium bromide catalysis, cyclization of **5b** yielded up to 60% **7b**, trans/cis ratio 8:1, and cyclization of **5c** to **7c** was <20%, trans/cis ~3:1. With 1 equiv of magnesium bromide, yields of **7c** were 80–90%, and some of the ¹³C NMR peaks attributed to the diastereomer appeared to be absent in the crude sample, though the possibility of a ~10:1 isomer ratio is not positively ruled out by our data. The strong diastereomeric preference for B trans to CN matches the stereocontrol found in acyclic reactions of α-bromo boronic esters with carboxylic esters⁶ or oxazolidinones⁷ and is supported by the NOE observations described below.

Cyclobutylboronic esters **7** are potentially useful for a wide variety of synthetic applications.² As a demonstration of the synthetic potential of this chemistry, the boronic ester group

of **7c** was replaced by an isopropenyl group by Zweifel's method⁸ to provide **8c**, which has a monoterpene carbon skeleton.

Function of Magnesium Ion. The effect of magnesium ion was especially surprising after zinc chloride had failed to catalyze ring closure in an earlier experiment. Perhaps zinc chloride is a strong enough Lewis acid to form a complex with the cyano group of **6** and break the carbon–boron bond, resulting in reversion to **5** as its zinc keteniminate derivative.

Before the role of magnesium cation was recognized, it was observed that a very strict experimental protocol was required. It was essential that the LDA solution be added to the boronic ester **5**, not vice versa, and that the amount of LDA added must not exceed 1 equiv. A reaction followed by ¹H NMR showed only ~10% completion after 1 day, but ~80% after 4 days. These observations are consistent with the hypothesis that the magnesium diisopropylamide present in the fresh samples of LDA liberates magnesium halide as the reaction mixture becomes less basic. As the LDA ages, the magnesium cation is apparently sequestered in the dark precipitate.

The catalytic role of the magnesium halide in the ring contraction of **6** to **7** presumably involves complex formation between the departing chloride ion and the magnesium cation. The transition state may be analogous in principle, though not in all details, to that proposed for the rearrangement of (*B*-alkyl)(*B*-dichloromethyl)borates.⁹

1,2,3-Tri- and 1,1,2,3-Tetrasubstituted Cyclobutanes.

Our mode of construction of the cyclobutane ring allows other substitution patterns with full stereocontrol. 1,2,3-Trisubstituted cyclobutanes were prepared by starting from (bromomethyl)boronic ester **9**, which is easily prepared by the published method.¹⁰ Treatment of **9** with lithioacetonitrile yielded **10a** (R¹ = H), or **9** with lithiopropanenitrile yielded racemic **10b** (R¹ = CH₃). Transesterification of **10** with (*R,R*)-1,2-dicyclohexyl-1,2-ethanediol to form **11** was followed by reaction with (dichloromethyl)lithium to form α-chloro boronic esters **12**. Treatment of **12a** with methylmagnesium chloride led to **13a**. Reactions of **12b** with butyllithium or with lithium benzyl oxide led to **13b** and **13c**, respectively. (Dichloromethyl)lithium converted **13** to α-chloro boronic esters **14**. This work was done prior to our recognition of the role of magnesium halide in the ring closure, and treatment of **14** with LDA containing a small amount of magnesium diisopropylamide resulted in erratic yields of cyclobutanes **15** together with 5–10% of their diastereomers **16** (Scheme 2). The yield of **15a** was 62%, that of **15b** was 50%, and that of **15c** was 15–20%. Aside from possible future synthetic utility, the immediate significance of this work lies in the **15/16** pairs suitable for NOE studies.

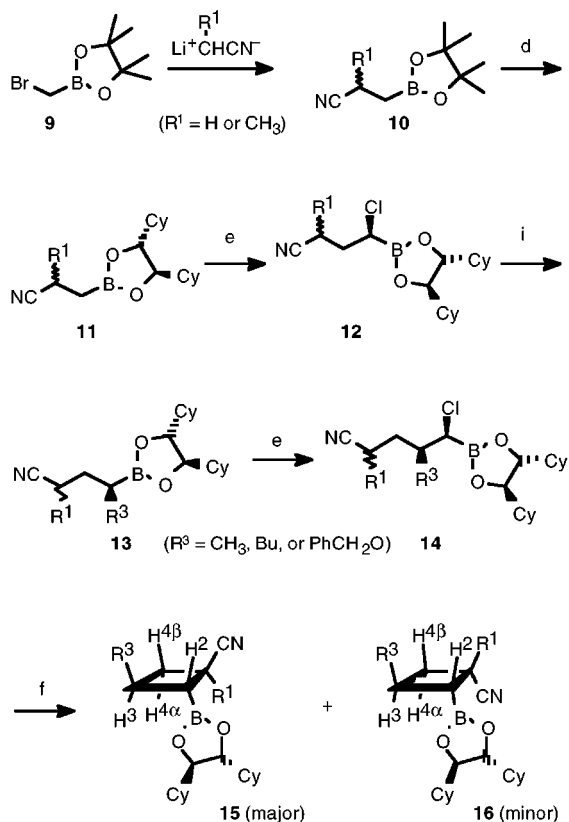
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Scheme 2^a

a: R¹ = H, R³ = CH₃; b: R¹ = CH₃, R³ = *n*-Bu; c: R¹ = CH₃, R³ = PhCH₂O

^a (d) (*R,R*)-1,2-Dicyclohexyl-1,2-ethanediol; (e) LiCHCl₂ in THF, -100 °C; ZnCl₂; to 25 °C 16–24 h; (f) LDA, -78 °C; 25 °C, 3 days; (i) RMgBr or RLi.

NOE Studies. The NOE spectra of major product **15a** (R¹ = H, R³ = CH₃) and its isomer **16a** support the structure assignments. Pure **15a** was obtained by crystallization, and a small amount of a 1:2 mixture of **15a** and **16a** was separated by chromatography. The 3-methyl and 1-H protons, assigned by chemical shifts and coupling constants, showed no NOE interaction in **15a** and a substantial NOE signal in **16a**, easily seen in the spectrum of the 1:2 mixture (see supplementary data) but not easily quantified. The other proton assignments for **15a** were consistent with a NOESY

spectrum and coupling constants calculated from an MMX program (PCModel) and formed a self-consistent NOE set.

NOE data for **15c** and **16c** (R¹ = CH₃, R³ = OCH₂C₆H₅) likewise support the structure assignments. The distinctive CHOR peak at δ 4.15 in **15c** [H^{3α}] showed a 1.9–3.1% NOE with the methyl singlet at δ 1.47 [CH₃^{1α}], and the corresponding peaks of **16c** [H^{3α} and CH₃^{1β}] showed no detectable NOE. The other ring hydrogens formed a self-consistent set, and the NOESY spectrum was consistent with the assignments.

There is nothing inherent in the foregoing synthetic method that would restrict the size to four-membered rings, which were chosen as our initial goal because they presented an interesting challenge for asymmetric synthesis.^{11,12}

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Supporting Information Available: Detailed preparative information for all new compounds; NOE data for **15a**, **16a**, **15c**, and **16c**, NOE spectrum of **16a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) **Typical Ring Closure (7c).** Chloro boronic ester **5c** was prepared according to the previously described method.^{1,2} Crude **5c** (14.2 g, 0.0278 mol) in THF (200 mL) was stirred at -78 °C during the dropwise addition of LDA and for an additional 30 min. Magnesium bromide in THF (140 mL, ~0.2 M, from magnesium metal and 1,2-dibromoethane) was added slowly to the cold solution. The mixture was stirred for 3 days at 20–25 °C (until monitoring by NMR indicated complete reaction). Aqueous workup followed by chromatography on a short silica column with 10% ethyl acetate in pentane yielded **7c**, *R_f* ~0.9, as an oil (12.36 g, ~95% **7c** with ~5% unchanged **5c** by ¹H NMR [δ 2.8, 3.95], 89% yield of **7c** contained): 300 MHz ¹H NMR (CDCl₃) δ 0.03 (s, 6), 0.85 (s, 9), 0.85–1.74 (m, 23), 1.97 (t, 2), 2.28 (m, 2), 2.4 (m, 2), 3.73 (m, 2), 3.83 (m, 2); 75 MHz ¹³C NMR (DEPT) (CDCl₃) δ -5.5 (CH₃), 18.2 (w, CSi?), 19.4 (CH₂), 25.75 (CH₃), 25.82 (CH₂), 25.90 (CH₂), 26.3 (CH₂), 27.3 (CH₂), 27.5 (CH₂), 32.8 (CH₂), 35.4 (w, CCN?), 38.4 (CH₂), 42.9 (CH), 60.1 (CH₂), 84.0 (CH), 125.0 (CN); CB (br) not observed. HRMS calcd for C₂₇H₄₈BNO₃SiN (MH⁺) 474.3574, found 474.3565. The analytical sample was further purified by chromatography. Anal. Calcd for C₂₇H₄₈BNO₃SiN: C, 68.48; H, 10.22; B, 2.28; N, 2.96; Si, 5.93. Found: C, 68.36; H, 10.17; B, 1.84; N, 2.82; Si, 5.84.¹¹

(12) All new compounds were characterized by 300 MHz ¹H and 75 MHz ¹³C NMR. Satisfactory elemental analyses for all elements present except O were obtained for **2**, **3a**, **4a**, **4b**, **7a**, **7b**, **7c**, **11a**, **13a**, **13b**, **15a**, **15b**, and **15c**. Satisfactory HRMS data were obtained for all of the foregoing, as well as **3b**, **3c**, **8c**, **10a**, **12a**, **13c**, **14a**, **14b**, and **14c**.

